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Neonatal Bilirubin Levels Following Administration of l-Triiodothyronine.* (24941)

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Association of prolonged jaundice with cretinism was noted by Christensen(1). He suggests that lack of thyroid hormone may delay hepatic enzyme maturation just as it delays maturation of ossification centers. When Christensen gave thyroid hormone to cretinous infants, there was a prompt fall in their serum bilirubin. His observations prompted us to undertake a study of the effect of thyroid substance on physiologic hyperbilirubinemia of the newborn. l-Triiodothyronine† was selected for administration to infants because of rapidity of its action.

Methods. Using the system of alternates, 100 test and 100 control infants were selected upon admission to nursery. All infants were normal, full term and were admitted to nursery from delivery. Each test infant was given oral dose of 25 μg of l-triiodothyronine daily for 4 days. Control infants were given no medication. Bilirubin determinations were done on each infant at 24-48 hours and 72-96 hours of age. Blood samples were drawn during morning hours by heel puncture technic. Bilirubin was measured by method of Hsia (2) as modified by C. C. Roby (personal communication). Levels of direct bilirubin were low, hence only total bilirubin was considered in calculations. The effect of l-triiodothyronine on bilirubin disposition was evaluated by comparing mean difference between first and second bilirubin levels in test and control groups, by comparing means of 24-48 and 72-96 hour specimens in test group with corresponding means in control group, and by comparing number of infants in each group who showed a rise in serum bilirubin during interval between the 2 determinations. Red cells of all infants were tested by direct Coombs technic for presence of blocking antibodies. ABO and Rh typings were done on all infants and their mothers.

Results. The mean difference between first and second bilirubin determinations in babies to whom l-triiodothyronine was given, was $+ 0.53 \pm 0.28$ mg/100 ml. The mean difference between the 2 specimens in control group was $+ 1.6 \pm 0.31$ mg/100 ml ($t = 7.0$; $p<0.01$). There was no evidence that the 2 groups differed in variability. Mean bilirubin level in test infants at 24-48 hours was 5.0 ± 0.25 mg/100 ml, range 0.8-12.2 mg/100 ml and at 72-96 hours was 5.5 ± 0.41 mg/100 ml, range 0.0-16.5 mg/100 ml. In control infants, the mean for first specimen was 5.8 ± 0.26 mg/100 ml (range, 0.8-13.4 mg/100 ml) and for second specimen, 7.3 ± 0.45 mg/100 ml (range, 0.6-19.3 mg/100 ml)

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† 1-triiodothyronine (Cytomel®) was generously supplied by Smith, Kline & French Lab.

TABLE I. Serum Bilirubin Levels in mg/100 ml at 24-48 Hr and 72-96 Hr of Age in Infants Given 25 μg of l-Triiodothyronine and in Controls.

	l-Triiodothyronine	Control*	p
Avg bilirubin, 24-48 hr	5.0 ±.25	5.8 ±.26	<.01
Idem 72-96 "	5.5 ±.41	7.3 ±.45	"
Avg diff. in bilirubin level between 1st and 2nd specimens	.53±.28	1.6 ±.31	"

* 100 infants.

(Table I). Forty-three of 100 test infants and 64 of 100 control infants demonstrated a rise in bilirubin during period between first and second determinations. $Chi^2 = 8.86$; p 0.005 (Table II). There was no evidence of bilirubin encephalopathy in any infant in the study.

The direct Coombs test was negative on all babies (Table III). There was a potential ABO incompatibility in 25 control and 22 test infants. This difference is not significant ($chi^2 = 0.25$; $0.5<p<0.7$).

Discussion. These results indicate that l-triiodothyronine exerts a depressant effect on serum bilirubin level of the newborn. This finding is consistent with Christensen's observation of the effect of thyroid hormone on prolonged neonatal jaundice in athyrotic infants. It is somewhat surprising in light of elevated levels of serum butanol extractable iodine found in newborns by Man(3) and Pickering(4). These investigators found neonatal BEI markedly elevated, reaching a peak at about 4 days of age. Van Middlesworth(5) observed an elevated I^{131} uptake during newborn period and suggested that newborn infants may undergo a period of physiologic hyperthyroidism.

The avidity of neonatal thyroid gland for iodine might also be increased by lack of thyroid substance in a form available for utilization. The elevated serum BEI might then be a reflection of the presence of thyroxine-like substances which are tightly bound by protein or otherwise inactivated and not available to the tissues.

TABLE II. Direction of Change of Bilirubin Level between 24-48 Hr and 72-96 Hr of Age in Control Infants and in Infants Given 25 μg of l-Triiodothyronine per Day.

	Infants with rising bilirubin	Infants with unchanged or falling bilirubin	Total
l-Triiodothyronine	43	57	100
Controls	64	36	100

$Chi^2 = 8.86$; $p < .005$.

Kurland(6) has suggested that tissues are more permeable to l-triiodothyronine than to thyroxine. It may be that in the newborn l-triiodothyronine can relieve a cellular deficiency of thyroid hormone and speed maturation of glucuronic acid conjugating system. Peterson(7) has shown an accelerated reduction and conjugation of compound F in thyrotoxic adults. Similarly in infants, excessive thyroid substance may speed the disposition of bilirubin.

Another possible explanation of our results is suggested by the effect of sulfisoxazole on serum bilirubin. Harris(8) found lowered bilirubin levels and marked increase in incidence of kernicterus in a group of premature infants who were given sulfisoxazole. Johnson (9) administered sulfisoxazole to rats congenitally deficient in glucuronyl transferase. The drug lowered the rats' bilirubin, increased the incidence of bilirubin encephalopathy and caused a marked intensification of bilirubin staining in fat and nervous tissue. Thus, it may be that l-triiodothyronine accomplishes a redistribution rather than an increased excretion of bilirubin.

TABLE III. Incidence of Possible Major Blood Group Incompatibility in Test and Control Infants.

	ABO incompatible	ABO compatible	Total
l-Triiodothyronine	22	78	100
Control	25	75	100

$Chi^2 = .25$; $.5 < p < .7$.

The decrease in serum bilirubin response to the dose of l-triiodothyronine used, was not large enough to be of clinical value. Furthermore, we have not eliminated the possibility that administration of the drug may increase rather than decrease incidence of bilirubin encephalopathy. Therefore, we do not recommend clinical use of l-triiodothyronine to control icterus neonatorum.

Summary. The effect of l-triiodothyronine on serum bilirubin in the newborn was

studied. The mean difference between bilirubin levels at 2 and 4 days of age was determined in 100 infants given 25 μg of l-triiodothyronine daily. This mean was compared with a similar mean in 100 controls. l-triiodothyronine significantly depressed the neonatal bilirubin level. The drug may exert its effect by accelerating maturation of glucuronic acid conjugating system.

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Diabetogenic Action of Analogues of 8-Hydroxyquinoline. (24942)

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As previously reported(1,2,3), some chelating agents for heavy metals have been shown to be diabetogenic in experimental animals. This effect may be attributed to their destructive action on the pancreatic islet cells by chelating with biologically important metallic ions. Further studies have been continued to detect other diabetogenic chelating chemical substances with structural similarity to 8-hydroxyquinoline. The present report deals with studies on the diabetogenic action of analogues of 8-hydroxyquinoline and derivatives of pteridine and similar structures with metal-binding properties.

Materials and methods. Adult rabbits were used. Blood sugar was determined by Hagedorn-Jensen's method(4) at various intervals after intravenous administration of the compounds. Histologic examination of pancreatic islet cells was performed with Gomori's chromium-hematoxylin phloxine method(5). Analogues of 8-hydroxyquinoline were used as solutions of sodium salts. Derivatives of pteridine were administered as aqueous solutions. Tested compounds and intravenously injected doses were as follows: 1-Hydroxyphenazine 30-60 mg/kg, 6-Hydroxy-m-phenanthroline (5:6-Pyridooxine) 30-70 mg/kg, l-Hydroxyacridine 20 mg/kg, 5-Hydroxybenzo-f-quinoline (5:6-Benzooxine) 30-50 mg/kg, 5, 8-Dihydroxyquinoxaline 50 mg/kg, 4-Hydroxypteridine 20 mg/kg, Isoxanthopterine 20 mg/kg, 2-Amino-4-hydroxypteridine 15-30 mg/kg, Picolinic acid 40-100 mg/kg, Dipicolinic acid 20-40 mg/kg.

Results. 1-Hydroxyphenazine caused a transitory hyperglycemia. However, doses over 60 mg/kg were intolerable, as they showed considerable toxicity. 1-2 hours after injection with doses 50-70 mg/kg of 6-Hydroxy-m-phenanthroline there ensued a remarkable hyperglycemia which returned to normal after 3-4 days (Fig. 1). Histologic examination of the pancreas of one rabbit which died 24 hours after injection revealed necrotic and degenerative changes of beta cells of the islets.

1-Hydroxyacridine also could produce a hyperglycemia as shown in Fig. 1. One rabbit died in convulsion 24 hours after administration of 1-hydroxyacridine (blood sugar 26 mg/100 ml). Histologic appearance of the islet of this animal showed degenerative changes of beta cells, while alpha cells remained almost normal. 5-Hydroxybenzo-f-quinoline caused similar hyperglycemia. However, degree of hyperglycemia was somewhat slighter than those produced with above 2